

BIOGRAPHICAL SKETCH

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NAME: Bruce J. Nicholson

eRA COMMONS USER NAME (credential, e.g., agency login): Nicholson

POSITION TITLE: Professor and Chair of Biochemistry

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Queensland, Australia	B.Sc.	1975	Biochemistry
University of Queensland, Australia	Honors	1976	Enzymology
California Institute of Technology, USA	Ph.D.	1983	Cell Biol/Neurobiology

Please refer to the Biographical Sketch sample in order to complete sections A, B, C, and D of the Biographical Sketch.

A. Personal Statement

I have served as Chair of Biochemistry at UTHSCSA for the last 10 years, served as President of the Association of Medical and Graduate Departments of Biochemistry in N. America from 2015-2016. The Biochemistry Department serves as the major focus of structural biology approaches in the Health Science Center and also hosts 4 Institutional Core Facilities. I served for 4 years on the Executive Committee of the Cancer Therapy and Research Center (CTRC) and currently serve on its Internal Advisory Board, and on the Leadership Council of the Institute for Integration of Medical Sciences funded by a CTSA award from NIH. I am the **co-founder and co-Director of the Center of Innovative Drug Discovery (CIDD)** that provides a critical link to bring bench discoveries to the clinic by hosting centralized facilities for high throughput and content screening (at UTHSCSA) and medicinal chemistry (at UTSA). This center has played a critical role in bringing in over \$14 M in extramural funds over the last 3 years, including a \$4.5M CPRIT grant to support growth of the facility at both UTHSCSA and UTSA.

My own laboratory seeks a comprehensive understanding of how the intercellular channels of gap junctions affect cellular functions in a variety of systems. Much of this work has focused on defining how the gating and permeability properties of these channels vary with the protein composition of the channels [reviewed in (1)], and how their function as mediators of direct intercellular communication impacts pathogenic processes in cancer, heart arrhythmias, neurological disorders and inflammatory responses to infection. Most recently, we have discovered the mechanism that underlie the long observed suppression of transformed cell growth by gap junction communication by redistribution of cAMP gradients established during the cell cycle (2). We have also described the molecular basis of how gap junction coupling can also influence motility of cells, and thus contribute to their metastatic potential (3). Current projects include collaborative efforts to investigate: the role of gap junctions in breast cancer metastasis to the bone, including the influence of direct intercellular miRNA exchanges between cancer cells and the target tissue (CPRIT grant with Jean Jiang); how gap junction coupling between endometrial and mesothelial cells cause enhanced invasiveness in endometriosis (SOM Pilot grant with Nameer Kirma), and; the potential role of gap junctions in propagating miRNA transfer between cell populations in the brain and how this contributes to the spread of neuronal damage in Alzheimer's Disease (NIA grant with Dr. Alex Pertsemidis)

1. Sosinsky GE, **Nicholson BJ**. Structural organization of gap junction channels. *Biochim. Biophys. Acta* 1711:99-125. (2005) *(Top 5 downloaded paper in 2005)*
2. Chandrasekhar, A., Kalmykov, E., Polusani, S.R., Mathis, S., Zucker, S., and **Nicholson, B.J.** Intercellular redistribution of cAMP through gap junctions underlies the selective suppression of HeLa cell growth by Cx26 *PLoS ONE* 8(12): e82335. doi:10.1371 (2013)

3. Polusani, SR, Kalmykov, EA, Chandrasekhar, A, Zucker, SN and **Nicholson BJ**. Connexin 26 gap junction coupling selectively contributes to reduced adhesivity and increased cell migration. *J. Cell Sci.* 129:4399-4410 (2016) PMID 27777264

B. Positions and Honors

Positions and Employment

1983 - 86	Postdoctoral Research Fellow, Dept. of Chemistry, California Institute of Technology
1986 - 93	Assistant Professor, Department of Biological Sciences, SUNY at Buffalo
1993 - 97	Associate Professor, Department of Biological Sciences, SUNY at Buffalo
1994 - 95	Associate Chair, Department of Biological Sciences, SUNY, Buffalo
1992 - 94	Director, Graduate Program in Molecular Cell Biology at SUNY, Buffalo
1994 - 97; 99 - 04	Co-Director, Ctr. for Advanced Molecular Biology and Immunology , SUNY Buffalo
1997 - 04	Professor, Department of Biological Sciences, SUNY at Buffalo
2000 -	Adjunct Professor, Department of Biological & Chemical Engineering, SUNY, Buffalo
2004 -	Chairman and Professor, Biochemistry , U. Texas Health Sci. Ctr. in San Antonio (UTHSCSA)
2005 -	Cross-appointed Professor, Dept. Physiology, UTHSCSA
2011 -	Founder/Co-Director - Center for Innovative Drug Discovery , UTHSCSA-UTSA
2015 - 2016	President – Association of Medical and Graduate Departments of Biochemistry

Honors/Memberships

1988 – 92	PEW Scholar
1992 - 97	AHA Established Investigator
1993 - 96	Max Planck Prize
1994 - 98; 99	Member CBYI (CDF4) Study Section (NIH)
1996	Organizer Keystone Conference on Intercellular Junctions
2001 – 05	Editor-in Chief: Cell Communication and Adhesion
2003 - 05	Member, Faculty of 1000
2003 -	Member, Council for Canadian Chairs
2006 -	Chair – Pew and Searle Scholars Selection Committee, UTHSCSA
2008 - 2012	Executive Committee – Cancer Therapeutics and Research Center (CTRC), UTHSCSA
2010 - 2011	Chair – Recruitment and Retention Committee, CTCR, UTHSCSA
2011 -	Member of Faculty Council – UTHSCSA School of Medicine
2012 -	Internal Advisory Board – CTCR, UTHSCSA
2013 -	Member, Executive Com. on Graduate Studies – Integrated Biomedical Sciences Program
2014 -	Recruitment Committee for Integrated Biomedical Sciences Program
2012 – 2018	Board Member - Association of Medical and Graduate Departments of Biochemistry

C. Contribution to Science

1. Identification of the connexin family and establishing its diverse nature

My major initial contribution to the gap junction field was the isolation of gap junction fractions from several tissues, and obtaining the first protein sequences that established that there was a family of proteins (connexins) with differential patterns of expression (4,5). Incidentally, this work also identified the first member of the Aquaporin family (AQP0), which subsequently was identified as the water channels in many systems (4). My lab then went on to clone the second connexin member (6), and develop techniques for their expression in *Xenopus* oocytes that allowed us to characterize the diverse properties of different members of the family (Cx 26, 32, 43, 37, 40, 30.3 and 31.1) in terms of gating and permeabilities (summarized in (7)).

4. **Nicholson BJ**, Takemoto LJ, Hunkapiller MW, Hood LE, Revel JP. Differences between liver gap junction protein and lens MIP 26 from rat: implications for tissue specificity of gap junctions. *Cell* 32:967-978. (1983)
5. **Nicholson BJ**, Dermietzel R, Teplow D, Traub O, Willecke K and Revel JP. Two homologous proteins of hepatic gap junctions *Nature*;329:732-734.(1987)
6. Zhang JT, **Nicholson BJ**. Sequence and tissue distribution of a second protein of hepatic gap junctions, Cx26, as deduced from its cDNA. *J Cell Biol* 109:3391-3401.(1989)
7. Yeager, M. and **Nicholson, B.J.**. Structure and Biochemistry of Gap Junctions *Curr. Opinions Struct. Biol.*6:183-192. (1996)

2. Description of the molecular basis of gap junction and hemichannel gating and its role in disease

The identification of a number of connexins and the characterization of their properties placed our lab in an excellent position to use comparative and mutagenic studies, along with functional analyses of the channels to dissect the molecular mechanisms underlying their regulation. We specifically focused on conserved sites in M1 and M2 that are important for channel gating, demonstrating that a conserved Proline (P87) in M2 is a critical mediator of voltage gating through propagating conformational changes within the protein (8). Recently we have gone on to use scanning cysteines mutagenesis and accessibility (SCAM) to map the site within the protein where the channel closes (Skerrett et al, in prep). We have also used functional analyses of disease associated mutants to understand their induced phenotype, such as why some mutants (e.g. Cx26M34T) have been described as both dominant or recessive in different patients (10), or why different mutants at the same site (e.g. A88, adjacent to the proline above) can lead to skin disease, deafness, or both (Xu et al, in prep). The former depends on the relative dosage of the heterozygotic WT gene, while the latter relates to different effects on gating of hemichannels that have distinct effects in different tissues as the dominant gating mechanisms vary based on the tissue environment. In addition to electrical gating mechanisms, we have also investigated the distinct mechanisms involved in chemical gating in response to phosphorylation, which we showed can occur through the “ball and chain” type mechanism (9) first described in K⁺ channels. We have also demonstrated that multiple signal mechanisms coordinate to close Cx43 channels, creating a “fail safe” system for controlling gating (10).

8. Suchyna TM, Xu LX, Gao F, Fournier CR, **Nicholson BJ**. Identification of a proline residue as a transduction element involved in voltage gating of gap junctions. *Nature* 365:847-849. (1993)
9. Zhou L, Kasperk EM, **Nicholson BJ**. Dissection of the molecular basis of pp60(v-src) induced gating of connexin 43 gap junction channels. *J Cell Biol* 144:1033-1045. (1999)
10. Skerrett IM, Di WL, Kasperk EM, Kelsell DP, **Nicholson BJ**. Aberrant gating, but a normal expression pattern, underlies the recessive phenotype of the deafness mutant Connexin26M34T. *FASEB J* 18:860-862. (2004)
11. Mitra, S., Xu, J. and **Nicholson, B.J.** Co-regulation of multiple signaling mechanisms in pp60v-src induced closure of Cx43 Gap junction channels. *J. Memb. Biol.* 245: 495-506. (2012) PMID: 22965738

3. Demonstration of variation in permeability between gap junction channels composed of different connexins, and selectivity for natural permeants

As a major function of connexins is to form intercellular channels, a critical question has been to define the permeability characteristics of the channels. Our lab has contributed to these efforts by initially showing that different connexins can impart different ion selectivity characteristics on the channels and that opposing two hemichannels with different ion selectivities can be one mechanism that creates rectifying channels (9). We have also gone on to show that different connexin channels have very different size cut-offs (11) and that the rates of permeant flux through them can only be accounted for if one assumes interactions of the permeants with the pore wall, using a PNP model of ion flux (11,12). A logical extension of this is that these channels should also show selectivity for natural permeants, and we were the first to show this was the case by capturing and characterizing radiolabeled metabolites passing between cells (10). More recently we have gone on to document that these channels can distinguish between quite subtle variations between metabolites, such as AMP and cAMP (Toloue, under revision).

9. Suchyna TM, Nitsche JM, Chilton M, Harris AL, Veenstra RD, **Nicholson BJ**. Different ionic selectivities for connexins 26 and 32 produce rectifying gap junction channels. *Biophys J* 77:2968-2987. 1999
10. Goldberg GS, Lampe PD, **Nicholson BJ**. Selective transfer of endogenous metabolites through gap junctions composed of different connexins. *Nat Cell Biol* 1:457-459. 1999
11. Weber PA, Chang HC, Spaeth KE, Nitsche JM, **Nicholson BJ**. The permeability of gap junction channels to probes of different size is dependent on connexin composition and permeant-pore affinities. *Biophys J* 87:958-973. (2004).
{cover photo}
12. Nitsche JM, Chang HC, Weber PA, **Nicholson BJ**. A transient diffusion model yields unitary gap junctional permeabilities from images of cell-to-cell fluorescent dye transfer between *Xenopus* oocytes. *Biophys J* 86:2058-2077. (2004)

4. Structural characterization of the gap junctional channel and its docking interface

As in the gating description above (#2), we have always had a strong interest in defining the underlying structures that dictate the varying properties we have measured in gap junctions, as this is one of the only ways one can understand the physics, and ultimately develop possible therapeutics. Our first effort in this regard was to attempt to understand the structures of the docking domains where the two hemichannels from each cell meet to form the full length gap junction. This is a unique docking structure and by using a series of movements of cysteines within the extracellular loops, we were able to map the manner in which the cysteines form intramolecular disulfide bonds

(13). The pattern of cysteines movements that rescued channel function demonstrated that these served to lock the structure into a β -sheet conformation required for docking, a deduction that has been borne out over 10 years later with the first higher resolution structure. We went on to identify the pore lining regions, which we did using cysteines substitutions along the transmembrane domains and probing for accessibility to thiols that would block the channel. We identified two helices that line the pore (14), as well as interactions between the helices that appear to be involved in gating (15). We have also gone on through collaborations with the late Gina Sosinsky to examine the structures of the N-termini that appear to be involved in some forms of voltage gating (16).

13. Foote CI, Zhou L, Zhu X, **Nicholson BJ**. The pattern of disulfide linkages in the extracellular loop regions of connexin 32 suggests a model for the docking interface of gap junctions. *J Cell Biol* 140:1187-1197. 1998

14. Skerrett IM, Aronowitz J, Shin JH, Cymes G, Kasperek E, Cao FL, **Nicholson BJ**. Identification of amino acid residues lining the pore of a gap junction channel *J Cell Biol* 159:349-360. (2002). *{Editorial "In this Issue" by Alan Dove; cited in Faculty of 1000}*

15. Toloue MM, Woolwine Y, Karcz JA, Kasperek EM, **Nicholson BJ** and Skerrett IM. Site-directed mutagenesis reveals putative regions of protein interaction within the transmembrane domains of connexins *Cell Commun Adhes* 15:95-1058. (2008).

16. Oshima, A., Tani, K., Toloue, M.M., Hioaki, Y., Smock, A., Inukai, S., Cone, A., **Nicholson, B.J.**, Sosinsky, G.E. and Fujiyoshi, Y. Asymmetric configurations and N-terminal rearrangements in connexin26 gap junction channels. *J. Mol. Biol.* 405: 724-735 (2011)

A full listing of publications can be seen at: (91 publications; H-index: 48; 58 cites per article)

<http://www.ncbi.nlm.nih.gov/sites/myncbi/bruce.nicholson.1/bibliography/48635002/public/?sort=date&direction=ascending>

D. Research Support

ACTIVE

UTHSCSA-SOM Translational Women's Health Initiative (Nicholson PI; Kirma Co-PI) 9/1/16 – 8/30/17

"A novel therapeutic strategy in endometriosis-gap junctions as mediators of invasiveness"

Testing patient samples for mechanism of gap junction induction in endometriosis and its role in invasiveness

Role: PI

NIH/NIA – P30 AG013319-22 S1 (Nicholson PI; Pertsemliadis Co-PI) 9/1/16 – 6/30/17

"miRNA expression and dissemination in the progression of Alzheimer's disease"

Funds an exploratory project to investigate the role of miRNA dissemination through gap junctions in the etiology of cancer; includes a subcontract to UT Dallas.

Role: PI

CPRIT – Core Facility Support Grant (McHardy – UTSA PI; Nicholson – UTHSCSA PI) 9/1/16 – 8/30/21

"Center for Innovative Drug Discovery: Enhancement of a Shared Cancer Resource in South Texas"

This is a \$4.6 million grant for development of the Center for Innovative Drug Discovery, co-founded by Dr. Nicholson. The grant was awarded through UTSA under Dr. McHardy, but 50% of the funds come to UTHSCSA to support the High Throughput Screening facility. UTSA provides the Medicinal Chemistry facility that together with HTSF, make up the CIDD.

Role: PI of UTHSCSA component

CPRIT - RP140644 (Nicholson PI; Jiang Co-PI) 8/1/15 – 5/31/17

"Inhibition of breast cancer metastasis to the bone by microRNA transmission through gap junctions"

This is a High Impact/High Risk Award that uses transgenic mouse models of breast cancer metastasis to the bone to explore the role of microRNAs in the suppression, or long-term latency, of these metastases, and the mechanism of microRNA transfer through gap junction channels.

Role: PI

Zealand Pharma - 130114 (Nicholson PI) 5/1/13 – 8/31/17

"Characterization of next generation peptides to open Cx43 channels"

This is a contract with a Danish biotech company for testing and characterizing peptides that positively modulate the activity of different connexins. We have developed a high throughput screen for peptides that inhibit or enhance coupling, and can use the peptides identified in other funded studies

Role: PI

NIH/NEI - RO1EY012085 (Jiang PI)

9/1/12 - 8/31/17

"Intracellular communication in the eye lens"

The major objective of this grant is to understand the roles of connexins in maintaining lens transparency and homeostasis, and cell protective function against UV radiation and oxidative stress. Our role was to provide electrophysiological expertise for characterization of channel properties

Role: Co-investigator

NIH/NCATS UL1TR001120-01/ KL2TR001118-01/ TL1TR001119-0 (R. Clark PI)

9/26/13 - 4/30/18

"Institute for Integration of Medicine & Science: A Partnership to Improve Health"

Major goals: To achieve optimal integration of clinical and translational research, education, training, and career development at UTHSCSA and partner organizations in South Texas. Existing and newly developed resources (e.g. drug discovery) will be focused on advancing clinical and translational research.

Role: Director of Drug Discovery Initiative

PREVIOUS 3 YEARS

NIH/NIAID - R15 AI101920 (Murthy PI; Nicholson PI subcontract)

7/1/13 – 6/30/16

"Mechanism(s) of CD8 T cell-mediated Chlamydia-induced reproductive pathology"

This grant seeks to test the model of how gap junction transfer of chlamydial antigens between oviduct cells results in collateral damage from the immune response that may underlie many of the major complications of chlamydial infections. Our role is to perform the in vitro assays to demonstrate peptide transfer and characterize the peptides transferred.

Role: Subcontract-PI

UTHSCSA School of Medicine (Nicholson/Kirma PIs)

7/1/14 – 6/30/15

"Endometriosis and the role of connexins"

This was a pilot grant to support accumulation of preliminary data on the unexplored role of gap junctions in the pathogenesis of endometriosis, and how this may be regulated by raf-1 signaling, in order to convert a 16th percentile R21 application into a fundable RO1 application.

Role: PI

IIMS – TTR Core usage grant (Nicholson, PI)

3/1/14 – 2/28/15

"Prevention of cellular uncoupling during the cell cycle as a broad spectrum cancer therapeutic strategy"

This was a grant to support high throughput screening in the CIDD Facility to enable a search for modulators of gap junctional coupling during the cell cycle as a potential therapeutic.

Role: PI

Zealand Pharma 201012 (Nicholson PI)

10/1/12 – 6/30/13

"Peptide strategies targeting Cx36 for Diabetes"

This was a contract with a Danish biotech firm for testing petidomimetic antagonists of Cx36 for possible application in treating diabetes

Role: PI

San Antonio Life Science Institute (Nicholson/Frantz: PIs)

4/1/12 – 9/30/13

"Center for Innovation in Drug Discovery"

This award provided significant funding for the founding of the Center for Innovative Drug Discovery, and initial pilot grants to multiple investigators to initiate screening and medicinal chemistry projects.

Role: Joint PI and Co-Director

Research Program for Xiangya Students – Dr. Bruce J. Nicholson

The Nicholson lab has been investigating the molecular basis of intercellular communication through gap junctions for 30 years, and has made significant contributions to our understanding of the structure and properties (1) of these ancient forms of communication between cells. This includes their regulation and gating by kinases, particularly those involved in the growth regulation of cells (2, 3). We have also demonstrated that these channels can be quite selective for metabolites (4), distinguishing between structurally similar, but functionally distinct molecules like AMP and cAMP. They can even allow large molecules like microRNAs and short peptides to transfer between cells.

More recently, the lab has been using our knowledge of these channel properties to understand the underlying mechanisms by which they suppress tumor cell growth (5), but at the same time can promote their migratory and invasive behaviors (6). Two projects currently ongoing in the lab are related to this invasive behavior induced by gap junction coupling, and its physiological consequences.

PROJECT 1: Gap Junctions and Invasiveness in Endometriosis:

Endometriosis, a major contributor to infertility and pelvic pain in women, results from retrograde menstruation through the fallopian tubes followed by establishment of endometrial tissue lesions on the peritoneum and other organs within the pelvic cavity. Hormonal therapies to control the symptoms of endometriosis remain the only recourse to date, due to a lack of understanding of the underlying molecular mechanisms that trigger the disease. Through comparisons of patient samples with those from normal subjects, we have noticed that gap junction expression profiles are altered in endometriosis. While RNA and protein are expressed at higher levels, the protein is trapped inside the cells. However, on exposure to mesothelial cells from the ovary or peritoneum, coupling between the endometrial and mesothelial cells is induced, and this is shown to promote the invasiveness that is characteristic of endometriosis. We are currently working to determine in which cells of the endometrium the gap junction expression changes, and if this is due to epigenetic modification of the connexin genes that encode gap junction proteins. Having demonstrated that the induction of coupling between endometrial and mesothelial cells is required for invasiveness, we are now determining what signals cause this induction and why are they specific to endometriosis. These signals would be ideal targets for developing novel drug therapies to combat this disease, without using hormones. Finally, we are expanding our comparisons of clinical tissues to determine how endometriosis, an invasive but benign condition, differs from endometrially-derived cancers.

PROJECT 2: Gap Junction Roles in Breast Cancer Metastasis to the Bone

Breast cancer mortality results, in 90% of cases, from metastatic spread of the disease, for which there are currently no good treatments. Bone is a common target for breast cancer metastasis, but recent studies have indicated that the bone microenvironment can affect metastasis. The host tissue can suppress cancer metastatic lesions, potentially explaining the long latent period between primary breast cancer diagnosis and manifestation of metastatic disease. We have observed that gap junction expression in the bone can suppress metastasis formation in mice, while others have noted that microRNAs have been seen to transfer between bone cells and cancer cells. We are currently testing in mice and in vitro, the hypothesis that growth-suppressing microRNAs generated in bone cells transfer to breast cancer cells when they form heterologous gap junctions, leading to suppression of metastasis. Understanding this process, and its underlying mechanisms, could provide a tool to help the body prolong the latent period prior to metastasis formation, perhaps indefinitely, by helping the body's own defenses to more effectively combat cancer.

1. Sosinsky GE, **Nicholson BJ**. *Biochim. Biophys. Acta* 1711:99-125. (2005) (*Top 5 downloaded paper in 2005*)
2. Zhou L, Kasperek EM, **Nicholson BJ**. *J Cell Biol* 144:1033-1045. (1999)
3. Mitra, S., Xu, J. and **Nicholson, B.J.** *J. Memb. Biol.* 245: 495-506. (2012) PMID: 22965738
4. Goldberg GS, Lampe PD, **Nicholson BJ**. *Nat Cell Biol* 1:457-459. 1999
5. Chandrasekhar, A., Kalmykov, E., Polusani, S.R., Mathis, S., Zucker, S., and **Nicholson, B.J.** *PLoS ONE* 8(12): e82335. doi:10.1371 (2013)
6. Polusani, SR, Kalmykov, EA, Chandrasekhar, A, Zucker, SN and **Nicholson BJ.** *J. Cell Sci.* 129:4399-4410 (2016) PMID 27777264